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Objective:

The central mission of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes is to determine how environmental, social, and host factors jointly contribute to health disparities. Specific aims of the Center are:

1. *To develop and operate an interdisciplinary children's health research center with a focus on understanding how biological, physiological, environmental, and social aspects of vulnerability contribute to health disparities;*
2. *To enhance research in children's health at Duke by promoting research interactions among programs in biomedicine, pediatric and obstetric care, environmental health, and the social sciences and establishing an infrastructure to support and extend interdisciplinary research;*
3. *To develop new methodologies for incorporating innovative statistical analysis into children's environmental health research and policy practice, with a particular emphasis on spatial, genetic and proteomic analysis;*
4. *To serve as a technical and educational resource to the local community, region, the nation, and to international agencies in the area of children's health and health disparities*; *and,*
5. *To translate the results of the Center into direct interventions in clinical care and practice*.

SCEDDBO leverages and promotes active partnerships among the Nicholas School of the Environment, the Duke University Medical Center, Trinity College of Arts and Sciences, and Duke's Children's Environmental Health Initiative, as well as the Durham County Health Department (DCHD), and the Lincoln Community Health Center (LCHC. The Center brings together the expertise of obstetricians, pediatricians, genetic epidemiologists, spatial statisticians, environmental scientists, social epidemiologists, social psychologists, geographers, and community organizations. SCEDDBO capitalizes on substantial ongoing commitments by Duke University to foster strong interdisciplinary research programs in environmental health sciences.

In all activities, SCEDDBO emphasizes the importance of diversity. The decision to focus on health disparities, the gender and racial diversity of Center leadership, the incorporation of natural, social and biomedical scientists, a commitment to community-based participatory research, and efforts to promote the careers of promising new investigators are all indicative of the importance that we place on fostering environments where all people can prosper.

Synthesis across SCEDDBO. **Research Project A: Mapping Disparities in Birth Outcomes** provides population-level research on health disparities in birth outcomes. Spatially-linking 1.7 million birth records with environmental, social, and host factor data layers allows for population-level analysis of potential co-factors identified in both the clinical obstetrics **Research Project B: Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in Birth Outcomes** and mouse model **Research Project C: Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health** studies. The data from Research Project A is spatially linked in GIS to the data from Research Project B.

The neighborhood assessment undertaken in Research Project B provides important neighborhood level environmental and social data to Research Project A. In addition, the environmental data developed for Research Project A works synergistically with the mouse model work in Research Project C. For example, the air quality data from Research Project A is being used to further refine experimental dose design in Research Project C. In turn, results from Research Project C regarding experimental effects of multiple environmental agents on fetal growth restriction and postnatal somatic and lung development help point to locations in North Carolina where we look more closely at air quality impacts on birth outcomes in Research Project A.

Thus Research Project A is an epidemiological study, while Research Project B is a complementary clinical obstetrics project. Both projects focus on how combined environmental, social, and host factors shape disparities in birth outcomes. Research Project B also allows for additional host factor analysis. Research Project C uses a mouse model system to explore how disparities in exposure and response to exposure initiate and/or enhance disparities in birth outcomes and subsequent neonatal respiratory health. Like Research Projects A and B, Project C explores the effects of *combined* environmental exposures to prototypical air pollutants common in North Carolina (particulate matter and ozone), as well as genetic background, on fetal growth restriction, neonatal somatic growth, and subsequent lung development and function.

Research Project A: Mapping Disparities in Birth Outcomes

Over the past year, the Project A research team has met both at full group level and in small groups to discuss new research ideas, review progress of current analysis, and identify next steps, and work on manuscript preparation.

Air Pollution. We have spent considerable time linking the detailed birth record data to USEPA PM_{10}, $PM_{2.5}$, and ozone monitoring data in order to study the impact of *maternal exposure to air pollution* on birth outcomes. Initial work built customary regression models to assess the linkage. We are especially focused on refining exposure metrics to more effectively characterize meaningful exposures, as well as to capture windows of vulnerability. Work continues on building *spatial downscalers*. Such modeling strategies enable the fusion of monitoring station data with computer model output to better assess environmental exposure. Then, we are using improved exposure assessment to examine linkage between exposure and adverse birth outcomes.

Racial Residential Segregation. Our project on *racial residential segregation* enables quantification of racial exposure/isolation at finer spatial scales within SMSA's. Such a measure can be connected to measures of social and economic disadvantage at these scales to gain insight into how racial residential segregation has manifested itself across urban landscapes. In turn, this promises to reveal key insights into how to think about the spatial aspects of the social factors influencing health disparities. We are working to determine which facets of segregation best characterize the way community-level racial residential segregation acts to promote health disparities in birth outcomes.

Environmental Contributions to Disparities in Pregnancy Outcomes. We published a review article on social and environmental contributors to disparities in birth outcomes based on both national and North Carolina data, as a way of compiling the many literatures we have accessed throughout our work on Project A. The manuscript, published in *Epidemiologic Reviews*, reviews research on how environmental exposures affect pregnancy outcomes and how these exposures may be embedded within a context of significant social and host factor stress.

Racial Disparities in Maternal Hypertensive Disorders. We analyzed data from North Carolina to determine how the pattern of maternal hypertensive disorders differs among non-Hispanic white, non-Hispanic black, and Hispanic women across the range of maternal ages. In addition we explored whether rates of poor birth outcomes, including low birth-weight and preterm birth, among hypertensive women differed by race.

Statistical Methods Development. Out of efforts to develop new spatial methodologies for addressing health disparities, additional methodological work on *disaggregated spatial modeling for areal unit categorical data* advanceed. This work uses innovative statistical methodology that extends spatial disease mapping techniques to model subgroups within areal units using a spatially smoothed, multilevel loglinear model. This work appeared in the *Journal of the Royal Statistical Society, Series C*. Another completed manuscript builds *joint models for birthweight and gestational age* using bivariate normal mixtures. Such joint modeling adjusts for maternal

risk factors and provides mixture analysis of the residuals to help illuminate further subpopulations with differential risk for adverse joint birth outcomes. It also avoids potential causal inference issues. Modeling of the mixture components is done through gestational age and then birthweight given gestational age. This work is forthcoming in *Statistics and Medicine*.

Spatial Quantile Regression. Novel work on spatial quantile regression has made substantial progress. We want to understand how dependence of response (birth weight) varies with quantile. Does the regression on median or mean birthweight look different from that for the 0.1 quantile? This is important given the greater interest in explaining low birthweight rather than in explaining average birthweight. Also, we expect quantile regressions to be more similar to each other when they are closer spatially than when they are farther apart. This requires the development of spatial quantile processes.

Flexible Bayesian Spatial Discrete-time Survival Model. In addition, we have developed a flexible Bayesian spatial discrete-time survival model to estimate the effect of environmental exposure on the risk of preterm birth. We view gestational age as time-to-event data where each pregnancy enters the risk set at a pre-specified time (e.g. the 32th week). The pregnancy is then followed until either (1) a birth occurs before the 37th week (preterm); or (2) it reaches the 37th week and a full-term birth is expected. As preliminary analysis, the methodology was applied to a dataset of geo-coded births in North Carolina in 2002. We estimated the risk of preterm birth associated with short-term exposure to fine particulate matter using air quality metrics derived from the EPA's Statistically Fused Air Pollution Database. We also conducted a simulation study and compared the proposed approach to the standard case-control and time series design.

Statistical Methods for Multivariate Spatial Data Measured on Different Scales. We are currently developing multivariate spatial models for birth outcomes measured on different quantitative scales. These outcomes include continuous variables, such as birthweight and gestational age; categorical variables, such as preterm birth and small for gestational age (SGA); and zero-inflated count variables, such as occurrences of medical complications. As part of our analysis, we are considering a variety of multivariate conditionally autoregressive (CAR) models, including multivariate intrinsic CAR models, multivariate proper CAR models, finite mixtures of CAR models, and Dirichlet process CAR models.

Publications – Accepted

Berrocal, V, Gelfand, A, Holland, D. A Spatio-temporal Downscaler for Output from Numerical Models. J*ournal of Agricultural Biological and Environmental Sciences,2009.*

Berrocal, V, Burke, JM, Gelfand, A, Holland, D, and Miranda, ML. On the Use of a $PM_{2.5}$ Simulator to Explain Eirthweight. Forthcoming, *Environmetrics*.

Berrocal, V., Gelfand, A., Holland, D. A Bivariate Space-time Downscaler under Space and Time Misalignment. Forthcoming, *Annals of Applied Statistics*.

Gray, S, Edwards, S, and Miranda, ML. Assessing Exposure Metrics for PM and Birthweight Models. *Journal of Exposure Science and Environmental Epidemiology, 2010, 20(5),* 469-477.

Schwartz, S., Miranda, ML., Gelfand, A. Joint Bayesian Analysis of Birthweight and Censored Gestational Age Using Finite Mixture Models. *Statistics in Medicine, 2010, 29 (16),* 1710-1723.

Tassone, E, Miranda, ML, Gelfand, A. Disaggregated Spatial modeling for Areal Unit Categorical Data. *Journal of the Royal Statistical Society,* 2010*, 59,* 175-190.

Future Activities

Achieving a better understanding of exposure to air toxins, as well as particulate matter and ozone, is a central focus of our future efforts. Areas of investigation will include space time analysis of trends in births across North Carolina, an investigation of linked births (same mother) using suitable random effects models, and a more thorough investigation of the impact of introducing spatial random effects in regression modeling to explain birth outcomes.

Supplemental Keywords

Data fusion, meta analysis, disparities, spatial disaggregation, spatial interpolation, spatial modeling, racial residential segregation

Research Project B: Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in Birth Outcomes

As of 4/30/10, 1738 women have been enrolled in the study. Women are recruited from Duke University Medical Center (DUMC) and the Durham County Health Department's prenatal clinic at Lincoln Community Health Center. Demographic data indicate that we are successfully recruiting women who are most at risk for adverse pregnancy outcomes, particularly low-income, low educational attainment, and non-Hispanic black women. We have been highly successful in collection of participant-level data as well as biological samples, with greater than 90% attainment of maternal blood sample for genetic and environmental analyses. Collection of cord blood and placental samples, which began in June 2007, has also been successful with approximately 763 delivery samples collected.

All maternal data are georeferenced (i.e., linked to the physical address of the mother) using Geographic Information System (GIS) software. The Healthy Pregnancy/Health Baby Study also draws on an in-depth neighborhood assessment designed to capture both built environment and community-level social stressors and community resources. The cohort study and neighborhood assessment data are spatially linked to extensive environmental and demographic data at a highly resolved spatial scale.

To date, we have generated genotypes on 1243 blood samples from pregnant women for 405 Single Nucleotide Polymorphisms (SNPs) in fifty-one genes. Candidate genes include those involving human environmental contaminant clearance (heavy metals and environmental tobacco smoke), infection and inflammation (cytokines, chemokines, and bacterial pathogen recognition), maternal stress response (serotonin), and other pathways that have been implicated as potential drivers of health disparities (vascular responsivity).

Statistical Methods Development. The project team continued to develop new ways of handling missing data in large epidemiological studies in which interaction effects are suspected. The main approach is to adapt regression trees to perform multiple imputation. This approach is being used to handle the missing data in the prospective study of Project B. This methodology has the potential to be utilized in a wide range of settings, including outside of epidemiological contexts.

The team examined approaches to performing Bayesian analysis after multiple imputation is used for missing data. This work is motivated by the use of the tree methodology for multiple imputation, because we are estimating Bayesian models with the completed datasets. The team developed methods for exploring sets of important predictors in large epidemiological studies when quantile regression will be used for the outcome variable. These methods adapt penalties from ordinary least squares lasso regression and elastic net regression so that they enable quantile regression. The team is using this methodology to explore the most important predictors of adverse birth outcomes in the Healthy Pregnancy, Healthy Baby Study.

The team developed an approach for performing Bayesian quantile regression with latent factors. Many of the predictors of adverse birth outcomes do not strongly predict adverse birth outcomes, likely because of the modest sample size for the strength of associations seen in the data. However, many of the predictors can be conceptualized as indicators of underlying factors that could be strong predictors; for example, several of the psychosocial variables can be grouped as a factor indicating the amount of social support available to the mother. We

developed and are applying methodology for estimating the effects of these factors on birth outcomes using the Healthy Pregnancy, Healthy Baby Study.

Psychosocial Indicators. Analyses have been completed on psychosocial influences on birth outcomes. The relationships among pregnancy intention, psychosocial health, and pregnancy outcomes have been examined. The influences of psychosocial health and smoking status have also been studied. In order to reduce the number of psychosocial variables, cluster analysis has been performed, resulting in three distinct clusters of women. These clusters are being examined in relation to other domains, such as genetics, personality, pregnancy outcomes.

*Environmental Sampling***.** Using the maternal environmental blood samples collected on all participants in Project B, we have been working to characterize maternal exposures to toxics. In addition to documenting the blood lead burdens among a cohort of pregnant women in Durham County, NC, we have been able to characterize current maternal exposures to lead by linking each participant to the tax parcel at which they resided during their pregnancy. We found that both year built and modeled lead exposure risk at participant's residence during pregnancy were not predictive of maternal blood lead levels. Taken in combination with results showing that maternal blood levels increased with age and parity, these findings indicate that maternal blood lead levels are much more likely the result of lead remobilization from historic exposures as opposed to contemporaneous exposures.

Community Assessment Project/Built Environment. The Community Assessment Project (CAP) assessed built environment variables for over 17,000 tax parcels, including the home addresses of over 40% of the participants in the Healthy Pregnancy, Healthy Baby Study (SCEDDBO Project B). Seven scales (housing damage, property disorder, security measures, tenure, vacancy, violent crime and nuisances) have been constructed at five levels of geography (census block, primary adjacency neighborhood, census block group, census tract and city-defined neighborhoods).

Publications – Accepted

Burgette, L. and Reiter, JP. Multiple Imputation via Sequential Regression Trees. Forthcoming, *American Journal of Epidemiology*.

Miranda, ML., Edwards, S., Paul, CJ., Swamy, G., Neelon, B. Blood Lead Levels among Pregnant Women: Historical Versus Contemporaneous Exposures, *International Journal of Environmental Research on Public Health, 7(4),* 1508-1519.

Swamy, GK, Garrett, ME, Miranda, ML, Ashley-Koch, AE. Maternal Vitamin D Receptor Genetic Variation Contributes to Infant Birthweight among Black Mothers. Forthcoming, *American Journal of Medical Genetics*.

Zhou, X. and Reiter, JP, (2010). A Note on Bayesian Inference after Multiple Imputation, *The American Statistician*, *64*, 159 - 163.

Future Activities

In the upcoming year, we will continue to enroll study participants with our new target sample size of 1800 pregnant women. We will continue analyses on approximately 1250 participants with complete pregnancy data, genetic results, and environmental results already in hand.

Analyses will look at the joint impact of environmental, social, and host factors on birth outcomes, especially as they differ by and within race. Identification of such co-exposures could lead to development and implementation of strategies to prevent adverse birth outcomes, ultimately decreasing or eliminating the racial disparity.

Supplemental Keywords
Pregnancy, preterm birth, low birth weight, racial disparity, African American, environmental stressors, gene-environment interactions, psychosocial stressors, genes, single nucleotide polymorphisms, genetic admixture

Research Project C: Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health

Progress Report/Summary of Accomplishments

1. Repeated exposures using spontaneously inhaled diesel particles generated from an internal combusion engine at US EPA have demonstrated dose-dependent augmentation on ozone-induced airway hyperresponsiveness.
2. This effect is sustained even after ceasing ozone exposure, since mice born to diesel exposed dams recovered for 4 weeks after neonatal ozone continue to demonstrate augmentation of airway hyperresponsiveness. This shows that prenatal diesel exposure has durable effects that persist to adulthood.
3. We have repeated the studies described above using diesel particles collected in collaboration with US EPA, and then instilled by tracheal insufflation during pregnancy, and found identical effects on fetal inflammatory cytokines in lung, placenta, and brain, as well as juvenile lung inflammatory cytokines. Most important, we found the same augmentation of ozone-induced airway hyperreactivity. This allows us to quickly move to more detailed analysis of the mechanism for pollutant effects without having to rely on ambient inhalation exposures, which cannot be accomplished at the desired rate because so many other investigators use the facilities.
4. In order to determine whether the effects of combined pollutant exposure on airway hyperresponsiveness is mediated by changes in neural or airway smooth muscle programming, we evaluated the effects of immediate postnatal ozone exposure on airway mechanics in anesthetized mice, as well as in tracheal explants. We found that the airway hyperresponsiveness was not attributable to large effects on either airway smooth muscle bulk or on intrinsic airway smooth muscle responsiveness to neurotransmitter or electrical stimulation. There were some trends towards delayed relaxation in the ozone-exposed group. We next repeated the studies in animals that underwent cervical vagotomy at 6 weeks (2 weeks recovery after the 4 weeks of intermittent ozone exposure) just before measurement of airway mechanics. *We found that vagotomy eliminated the ozone-induced airway hyperresponsiveness*. This represents a paradigm shift of our understanding of the mechanisms by which ozone might affect asthma in children.

Future Activities

1. Modification of study design: As noted above, the effects of resource deprivation suggested by findings in Projects A and B prompted us to add the resource deprivation (nesting restriction) component to Project C in order to test the proof-of-principle that the combination of multiple stressors/environmental contaminants may affect health even when the individual exposures do not.
2. Because the main findings in Project B pertain to fetal growth restriction and low birthweight, we are now designing studies in the animal model to mimic impaired uteroplacental insufficiency.

Publications – Accepted

Auten RL, Mason SN, Potts EN, Fischer BM, Huang Y, Foster WM. Maternal exposure to particulate matter increases postnatal ozone-induced airway hyperreactivity in juvenile mice. *Am J Resp Crit Care Med*. 2009. 180(12):1218-26. PMID 19762564

Auten RL and Foster WM. Biochemical Effects of Ozone on Asthma Development. Forthcoming, *Biochimica et Biophysica Acta*.

Supplemental Keywords
Airway hyperreactivity, diesel exhaust particles, air pollution, lung function